Immune thrombocytopenia associated with consumption of tonic water

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Thrombocytopenic purpura can develop from an induced antibody response that destroys platelets. Megakaryocyte production may also play a role. Although the inciting antigen is usually not identified, it is important to consider medications. This article presents the case of a man who developed sudden onset of severe thrombocytopenia associated with the ingestion of quinine-containing tonic water.

> If any of these few notes on the effects of quinine prove of any use to the profession, or add one drop to the ocean of science, the purpose of the writer will be fully answered. —W. H. Vipan, 1865 (1)

Thrombocytopenic purpura can be life threatening with severe complications when platelet counts fall below 25,000/uL. Treatment is directed at suppressing or eliminating the antibody response that destroys the platelets and/or the stimulus that impacts the production of platelets by megakaryocytes. Medications have been implicated in the aberrant antibody response and, in those cases, their identification is important in treatment and prevention of future episodes. The patient discussed herein developed a sudden and dramatic decline in peripheral platelet counts, possibly related to the consumption of tonic water.

CASE PRESENTATION

A 70-year-old man presented with a 2-day history of nosebleeds, mucosal bleeding, painful bruising of his tongue, and diffuse ecchymoses over his arms, legs, and trunk *(Figure 1)*. The previous week he had been seen for a routine checkup. At the time, he felt well, had a platelet count of 151,000/uL, a hemoglobin of 14.1 g/dL, a hematocrit of 42.3%, and no bleeding manifestations. In only 3 days, he developed diffuse bleeding, and his platelet count had dropped to 1000/uL. He was admitted to the hospital. During the 2 days prior to presentation, he had been celebrating with a friend, drinking beverages containing tonic water.

His estimated consumption of the tonic water alone was up to 80 ounces over 2 days. He had indulged in tonic water beverages previously and on a regular basis, though in more moderate quantities. He had a previous history of atrial fibrillation, hypertension, and hyperlipidemia. At age 67, he had replacement of his stenotic aortic valve by a bioprosthesis. There had been no antecedent infectious illnesses. He had stopped warfarin before admission due to the bleeding. Other medications included pravastatin, carvedilol, digoxin, quinapril, vitamin D, montelukast, and fluticasone.

On examination, the patient had diffuse bleeding into his buccal mucosa and posterior pharynx. His tongue was swollen, tender, and bruised. Petechiae and ecchymoses were present over his arms, legs, and trunk. The nasal mucosa was ecchymotic, with dried dark blood. The feces were melanotic and the fecal immunochemical test was positive. Laboratory results are shown in the *Table.* A peripheral blood smear demonstrated only sparse platelets *(Figure 2),* and bone marrow biopsy showed megakaryocytes, which were predominantly mature with focally increased cellularity *(Figure 3).* Flow cytometry showed no evidence of hematopoietic neoplasia, lymphoproliferative disease, or plasma cell dyscrasia.

The patient was treated with dexamethasone 40 mg daily for 4 days. His platelet count promptly rose. His bleeding resolved and ecchymoses subsided by the fourth day of admission, when he was discharged. His platelet count at discharge was 67,000/uL and was back in the normal range shortly thereafter. He has since resumed his previous medications, avoided tonic water, and has had no further episodes of thrombocytopenia.

DISCUSSION

Immune thrombocytopenia is defined as a platelet count of <100,000/uL with no evidence of leukopenia or anemia. The condition has been referred to as "idiopathic" but is more frequently called "immune" thrombocytopenic purpura (ITP), even though aspects of the pathogenesis are not always understood. Primary ITP is defined as cases with no clear underlying causation. Secondary ITP is the label affixed when a medication, infection, or other condition accounts for the abnormal

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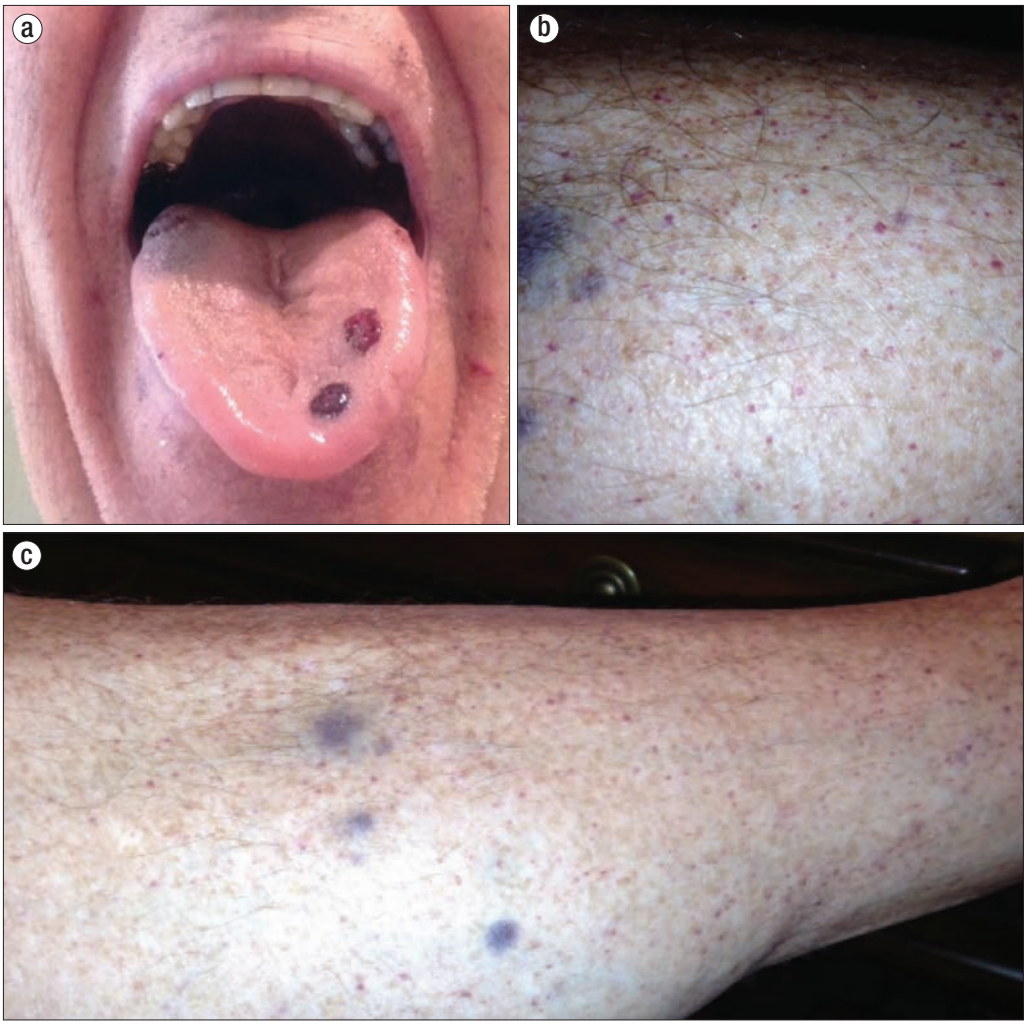

Figure 1. **(a)** Bruising of the patient's tongue. **(b)** Ecchymoses and petechiae of lower leg. **(c)** Ecchymoses and petechiae of upper arm.

antibody response (2). Various secondary causes of immune thrombocytopenia are listed in *Table 2*.

A positive test for antibodies would have made for a more convincing diagnosis, although it is known that the absence of such results cannot rule out a diagnosis of drug-induced immune thrombocytopenia (3). There had been a several-week delay in testing for these antibodies, which could have been a factor in the negative report. In addition, problems exist with standardization of testing. Antiplatelet antibodies are known to have low sensitivity and low specificity (4). The ability of laboratories to correctly identify the antibodies has been estimated to be in the range of 20% to 97% (5).

The low haptoglobin level in this patient suggests the possibility of hemolysis, although no significant schistocytes were seen on the peripheral blood smear *(Figure 2)*. The drop in hemoglobin was likely due to gastrointestinal blood loss implied by the positive fecal immunochemical test. Hemolytic uremic syndrome has been reported with quinine ingestion (6), although the absence of proteinuria, normal creatinine, and convincing hemolysis makes this diagnosis unlikely.

Thrombocytopenia, when it occurs due to quinine antibodies, is caused by a sensitization to quinine from prior exposure. Upon reexposure, antibodies develop to the drug or to metabolites of the drug. Importantly, and in contrast to primary ITC, platelet levels usually return to normal promptly when quinine is withdrawn. Primary "idiopathic" thrombocytopenia also behaves differently, with a slower onset (7). The rapid onslaught of severe thrombocytopenia in this case favors an antibody response to a medication or substance for which there had been prior sensitization. The patient's prompt rise in platelet counts and normal platelet counts since initial treatment also favor secondary ITP.

Purpura was first linked with quinine in a report on four patients in 1865 (1). Most cases today are idiopathic, but increasingly medications have been found to play a role. Quinine is reported to be one of the most frequent causes of drug-induced thrombocytopenia. It is thought to be able to bind to platelet membranes and then stimulate IgG antibodies. The antibodies result in destruction of platelets only when the drug is present, and they go away in the absence of the drug. As mentioned above, antibodies to nondrug metabolites can also result in thrombocytopenia and should be included in testing (8). Megakaryocytes may also bind with IgG in the presence of quinine, resulting in apoptosis, a decrease in cell viability and an increase in cell death of the precursor cells (9).

Quinine sulfate is derived from the bark of the Cinchona tree and has been used for centuries as a prophylaxis and treatment for the malaria parasite. Quinine is dissolved in carbonated water to produce tonic water. Sweeteners such as high-fructose corn syrup are often added in contemporary preparations. The taste of tonic water was originally quite bitter, but was more easily tolerated when mixed with gin. A daily "gin ration" was prescribed for the officers of the British East India Company in the 1700s. Winston Churchill, a fan of the gin and tonic drink, once proclaimed, "The gin and tonic has saved more Englishmen's lives, and minds, than all the doctors in the Empire" (10).

Other drugs were subsequently found to be more effective for malaria, but quinine has remained popular as a treatment for nocturnal leg cramps. At least one study has

Table 1. Laboratory results

Test	Result
Platelets (/uL)	1000
Hemoglobin (g/uL)	12.4
Hematocrit	35.7%
White blood cell count (/uL)	4200
Prothrombin time (sec)	13.8
International normalized ratio	1.4
Partial thromboplastin time (sec)	26.7
Thrombin time (sec)	17.6
Fibrin split products (ug/mL)	<5
D-Dimer (mg/L)	0.33
Reticulocytes	1.33%
Lactate dehydrogenase (U/L)	280 (normal: 85–245)
Haptoglobin (mg/dL)	<1
Direct bilirubin (mg/dL)	0.2
Sodium (mEq/L)	137
Potassium (mEq/L)	3.9
Chloride (mEq/L)	102
Carbon dioxide (mEq/L)	102
Blood urea nitrogen (mg/dL)	13
Creatinine (mg/dL)	0.8
Calcium (mg/dL)	8.5
Total protein (g/dL)	6.5
Albumin (g/dL)	3.8
Alkaline phosphatase (U/L)	60
Aspartate transaminase (U/L)	29
Hepatitis B surface antigen	Nonreactive
Hepatitis B surface antibody	Nonreactive
Hepatitis C core antibody	Nonreactive
Urinary protein	Negative
Direct Coombs	Negative
HIV	Negative
Quinine IgG	Negative
Quinine IgM	Negative
Quinine-associated antibodies IgG (nondrug)	Negative
Quinine-associated IgM (nondrug)	Negative

demonstrated its effectiveness (11). Others have cautioned its use for such purposes (12). All over-the-counter products containing quinine sulfate were banned by the US Food and Drug Administration on December 12, 2006. The ban included the announcement of "665 reports of adverse events with serious outcomes associated with quinine use, including 93 deaths" (13). A prescription preparation, Qualaquin, remains available in a 324 mg tablet. However, the Food and Drug Administration warned about its use for leg cramps in 2010, stating, "Qualaquin should not be used for night time leg cramps. Qualaquin use may result in serious and life-threatening hematological reactions" (14). With the absence of nonprescription quinine preparations and the strong caution to physicians about prescription Qualaquin, many have resorted to quinine-containing tonic water to ease troublesome leg cramps. This case suggests that tonic water to treat leg cramps, or for celebration, should be used in moderate doses, if at all.

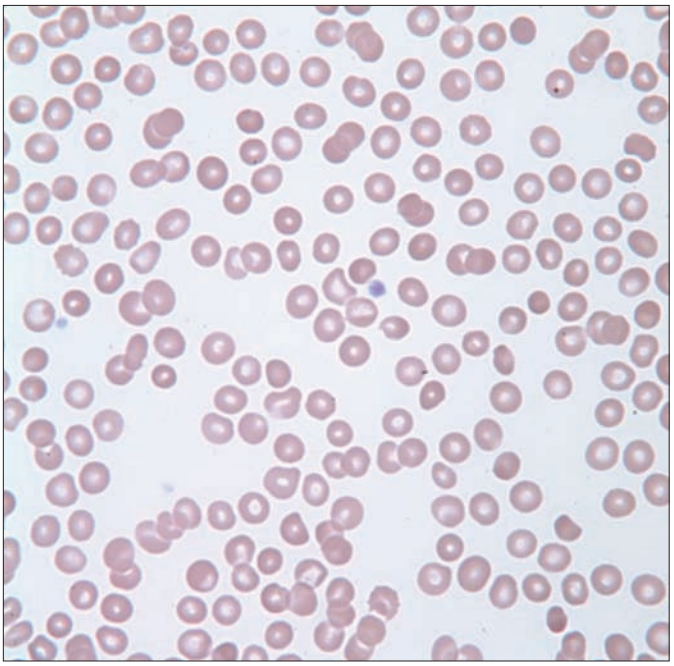

Figure 2. Peripheral blood smear demonstrating a paucity of platelets.

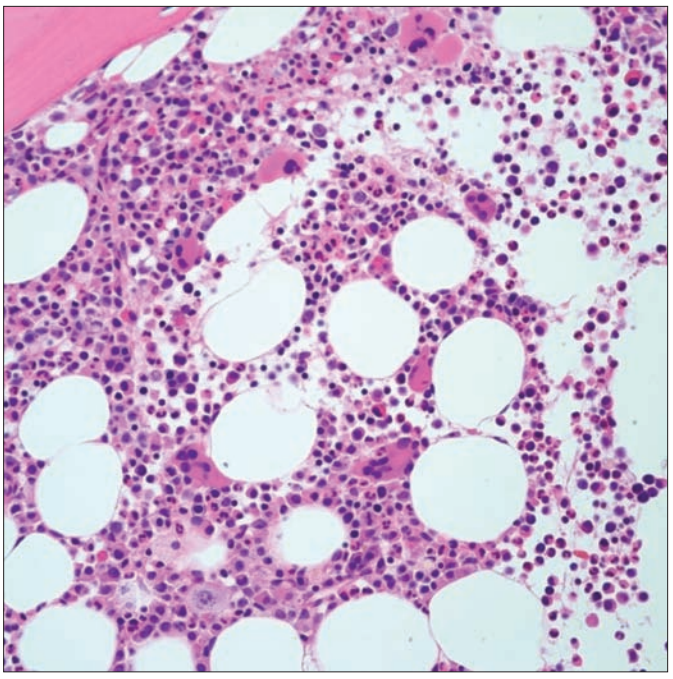

Figure 3. Bone marrow aspirate demonstrating abundant megakaryocytes with a focal increase in cellularity.

Table 2. Causes of thrombocytopenia*

Medications	Other causes
Acetaminophen	Antiphospholipid syndrome
Abciximab	Chronic lymphocytic lymphoma
Gold (15)	Hepatitis C virus
Ibuprofen	*Helicobacter pylori*
Levo-dopa	HIV
Naproxen	Non-Hodgkin's lymphoma
Penicillin (16)	Systemic lupus erythematosus
Procainamide	Wiskott-Aldrich syndrome
Quinine	
Quinidine	
Trimethoprim-sulfamethoxazole	
Vancomycin	

*From reference 4, unless otherwise indicated.

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